REMARKS

I. Status of the Claims

Claims 8, 10, 11, 13, 15, 18-27 and 35-55 are pending in the application. Claims 8, 10, 11, 13, 15, 18-27 stand rejected under 35 U.S.C. §102(e), and claims 35-55 stand rejected under 35 U.S.C. §103(a). The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

II. Rejections Under 35 U.S.C. §102(e)

A. Martuza '096

Claims 8, 10, 11, 13, 15 and 18-27 again stand rejected as anticipated by U.S. Patent 5,585,096 ("Martuza '096"). Applicants previosly submitted a declaration under 37 C.F.R. §1.131, establishing that the inventors had made the claimed invention in this country prior to the June 23, 1994 priority date of the '096 patent. The examiner has argued that the evidence submitted is insufficient to prove prior invention for the following reasons:

- the "species" shown in the evidence is "far narrower" than that claimed;
- no claims are limited to the use of the specifically named HSV-1 strain, replication competent HSV-1, HSV-1, or even treatment of human tumors
- no additional evidence is provided showing that one of skill in the art would view the evidence as indicating possession of the invention "as broadly claimed"
- there is insufficient evidence to demonstrate reduction to practice, or in the alternative, diligence until filing

Interestingly, the examiner cites only two cases in support of this rejection: (a) a D.C. Circuit case from 1897 that merely defines "conception"; and (b) *In re Fisher*, 166 USPQ 18, 24 (CCPA

1970), a case that deals neither conception nor the more salient issue of genus-species conceptions. To the contrary, applicants submit that the ***relevant*** case law provides that applicants' showing is more than sufficient evidence of prior invention.

The general rule as to proving conception of generic claims is as follows: "A reference or activity applied against generic claims may (in most cases) be antedated as to such claims by an affidavit or declaration under 37 CFR 1.131 showing completion of the invention of only a single species, with the genus, prior to the effective date of the reference or activity .... See *Ex parte Biesecker*, 144 USPQ 129 (Bd. App. 1964). See, also, *In re Fong*, 288 F.2d 932, 129 USPQ 264 (CCPA 1961); *In re Defano*, 392 F.2d 280, 157 USPQ 192 (CCPA 1968)." MPEP §715.02. Clearly, applying this rule, applicants have done all that is required to antedate Martuza.

However, the examiner has alluded to the fact that the claimed invention may fall within the realm of the "unpredictable arts," and thus implied that the general rule may not be applicable. MPEP §715.02 ("See, however, MPEP §715.03 for practice relative to cases in unpredictable arts."). Yet even MPEP §715.03 concedes that "References or activities which disclose one or more embodiments of a single claimed invention, as opposed to species of a claimed genus, can be overcome by filing of a 37 CFR 1.131 affidavit showing prior completion of a single embodiment of the invention, whether it is the same or a different embodiment from that disclosed in the reference or activity. See *In re Fong*, 288 F.2d 932, 129 USPQ 264 (CCPA 1961)." Because the examiner has made ***no attempt*** to parse out different issues of patentability for the rejected claims, ***by definition***, Martuzza discloses an embodiment of the claimed invention, not a species of a genus. As such, the possession of the same embodiment as Martuza – an γ34.5 defective HSV-1 – suffices for the purpose of antedating the reference,

unpredictability notwithstanding. Thus, yet again, applying the correct rule of law, applicants have met or surpassed that which is required for antedating the cited reference.

To summarize, whether or not this is "an unpredictable art," the evidence relied upon by applicants – combining an γ34.5 defective virus with radiation – is sufficient overcome Martuza, which allegedly teaches the same. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

B. Martuza '379

Claims 8, 10, 11, 13, 15 and 18-27 stand rejected as anticipated by U.S. Patent 5,585,096 ("Martuza '379"). Applicants previously submitted a declaration under 37 C.F.R. §1.131, establishing that the inventors had made the claimed invention in this country prior to the earliest possible priority date for the '379 patent, June 23, 1994. The examiner has argued that the evidence submitted is insufficient to prove prior invention for the reasons set forth above. Similarly, for the same reasons as given by applicants in the preceding rebuttal, it is again submitted that the examiner is incorrect and that the relevant legal standards mandate the opposite conclusion – that applicants were in fact in prior possession of the claimed invention. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

III. Rejections Under 35 U.S.C. §103(a)

Claims 35-55 remain rejected over U.S. Patent 5,846,945 ("McCormick '945") in view U.S. Patent 5,776,743 ("Frisch '743") and/or Martuza '096 or Martuza '379. Applicants continue to traverse the rejection on its merits for the reasons given in the previous responses, namely, that there is absolutely no scientific basis for combining the teachings of adenovirus and

herpesvirus references, as posited by the examiner. Moreover, given the substantive differences between the teachings of McCormick '945 and Frisch '743, one of skill in the art would ***not*** be motivated to make their combination.

However, in order to advance the prosecution, applicants previously submitted §131 affidavits to remove the Martuzza patents as references. The examiner appears to argue that, since the evidence provided was directed to HSV-1, it cannot be relevant to claims directed to adenovirus. Once again, the examiner is incorrect as a matter of law.

Under the rule set forth in *In re Stempel*, 113 USPQ 77 (CCPA 1957), an antedating affidavit may simply show possession of that subject matter disclosed by the prior art. Instructive is the discussion provided in MPEP §715.03:

> Where the only pertinent disclosure of the reference or activity is a single species of the claimed genus, the applicant can overcome the rejection directly under 37 CFR 1.131 by showing prior possession of the species disclosed in the reference or activity .... *In re Stempel*, 241 F.2d 755, 113 USPQ 77 (CCPA 1957).

Moreover, it is notable that the examiner, in advancing this rejection, finds that herpesvirus and adenovirus do not present issues of patentable distinction. This brings yet more relevant case law, also cited at MPEP §715,03, into play:

> Proof of prior completion of a species different from the species of the reference or activity will be sufficient to overcome a reference indirectly under 37 CFR 1.131 if the species shown in the reference or activity would have been obvious in view of the species shown to have been made by the applicant. *In re Clarke*, 356 F.2d 987, 148 USPQ 665 (CCPA 1966); *In re Plumb*, 470 F.2d 1403, 176 USPQ 323 (CCPA 1973); *In re Hostettler*, 356 F.2d 562, 148 USPQ 514 (CCPA 1966).

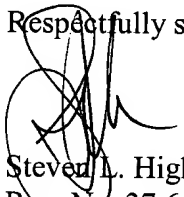
Because the examiner finds adenovirus and herpesvirus to both be rejectable over the Martuza patents, the showing of an HSV species is sufficient to establish possession of an invention drawn to adenovirus.

In light of these observations, reconsideration and withdrawal of the rejection is therefore respectfully requested. In contrast to the prior action, should the examiner maintain this rejection, applicants request a specific rebuttal of this argument, including reliance on ***relevant*** case law citations.

IV. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicted. Should Examiner Priebe have any questions regarding this response, a telephone call to the undersigned is invited.

Respectfully submitted,



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Date: July 7, 2003

APPENDIX A: CLEAN COPY OF PENDING CLAIMS (UNOFFICIAL)

8. The method according to claim 13, wherein the tumor cell is a human tumor cell.

10. The method according to claim 8, wherein the human tumor cell is a brain cancer cell.

11. The method according to claim 8, wherein the human tumor cell is a breast cancer cell.

13. A method of inhibiting growth of a tumor *in vivo* comprising delivering to said tumor, in combination, a herpes simplex virus and ionizing radiation, wherein said combination is sufficient to inhibit the growth of said tumor.

15. The method according to claim 13, wherein the herpes simplex virus is HSV-1.

18. A method of enhancing the effectiveness of ionizing radiotherapy comprising administering to a tumor site in a mammal (i) a pharmaceutical composition comprising a herpes simplex virus and (ii) ionizing radiation, wherein the combination of herpes simplex virus infection and radiation is more effective than ionizing radiation alone.

19. The method according to claim 18, wherein the composition comprises from about 10^8 to about 10^{10} herpesvirus particles.

20. The method according to claim 18, wherein the administering is by means of an oral or intravenous route.

21. The method according to claim 18, wherein the tumor is brain tumor or breast tumor.

22. The method according to claim 18, wherein the mammal is a human.

23. A method of killing a tumor cell comprising the steps of:

(a) contacting said tumor cell with a herpes simplex virus; and

(b) exposing said cell to a dose of ionizing radiation sufficient to kill said cell in conjunction with said herpes simplex virus.

24. The method according to claim 23, wherein the herpes simplex virus is HSV-1.

25. The method according to claim 13, wherein said delivering comprises injecting into a tumor site a pharmaceutical composition comprising said herpes simplex virus.

26. The method according to claim 13, wherein the tumor is exposed to ionizing radiation selected from the group consisting of X-irradiation, γ-irradiation and β-irradiation.

27. The method according to claim 13, wherein the tumor is a brain tumor or a breast tumor.

35. The method according to claim 46, wherein the tumor cell is a human tumor cell.

36. The method according to claim 35, wherein the human tumor cell is a brain cancer cell.

37. The method according to claim 35, wherein the human tumor cell is a breast cancer cell.

38. The method according to claim 46, wherein the tumor cell is located within an animal, and the adenovirus is administered to the animal in a pharmaceutically acceptable form.

39. The method according to claim 46, wherein the tumor cell is exposed to X-irradiation, γ-irradiation, or β-irradiation.

40. A method of inhibiting growth of a tumor *in vivo* comprising delivering to said tumor, in combination, an adenovirus lacking an exogenous therapeutic gene and ionizing radiation, wherein said combination is sufficient to inhibit the growth of said tumor.

41. A method of enhancing the effectiveness of ionizing radiotherapy comprising administering to a tumor site in a mammal (i) a pharmaceutical composition comprising a adenovirus lacking an exogenous therapeutic gene and (ii) ionizing radiation, wherein the combination of adenovirus infection and radiation is more effective than ionizing radiation alone.

42. The method according to claim 41, wherein the composition comprises from about 10^8 to about 10^{11} adenovirus particles.

43. The method according to claim 41, wherein the tumor is exposed to ionizing radiation selected from the group consisting of X-irradiation, γ-irradiation and β-irradiation.

44. The method according to claim 41, wherein the tumor is brain tumor or breast tumor.

45. The method according to claim 41, wherein the mammal is a human.

46. A method of killing a tumor cell comprising the steps of:

a) contacting said tumor cell with an adenovirus lacking an exogenous therapeutic gene; and

b) exposing said cell to a dose of ionizing radiation sufficient to kill said cell in conjunction with said adenovirus.

47. The method according to claim 46, wherein said delivering comprises injecting into a tumor site a pharmaceutical composition comprising said adenovirus.

48. The method according to claim 46, wherein the tumor is exposed to ionizing radiation selected from the group consisting of X-irradiation, γ-irradiation and β-irradiation.

49. The method according to claim 46, wherein the tumor cell is a brain tumor cell or a breast tumor cell.

50. The method according to claim 46, wherein the composition comprises from about 10^8 to about 10^{11} adenovirus particles.

51. The method of claim 40, wherein said adenovirus is Ad5.

52. The method of claim 41, wherein said adenovirus is Ad5.

53. The method of claim 46, wherein said adenovirus is Ad5.

54. The method of claim 41, wherein said composition is administered intravenously.

55. The method of claim 40, wherein said composition comprises from about 10^8 to about 10^{11} adenovirus particles.